

Review of olanzapine in the management of bipolar disorders

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Abstract: Olanzapine is an atypical antipsychotic currently with indications for the treatment of schizophrenia, acute mania and the prevention of relapse in bipolar disorder. A growing body of clinical evidence supports these indications. Acute mania trials have demonstrated superior efficacy of olanzapine to placebo, equal or superior efficacy to valproate and superior efficacy in combination therapy with lithium or valproate compared to mood stabilizer monotherapy. Olanzapine demonstrated a modest effect in the treatment of bipolar depression with a substantially enhanced effect in combination with fluoxetine. Maintenance trials showed olanzapine to be more efficacious than placebo in the prevention of manic and depressive relapses and non-inferior to lithium or valproate. Combination of olanzapine with lithium or valproate was also found to be more efficacious than lithium or valproate monotherapy in the prevention of manic relapse in patients with a partial response to monotherapy with lithium or valproate. These trials suggest that olanzapine is a viable option and an invaluable addition to the pharmacological armamentarium in the treatment of bipolar I disorder. However, this can often be mitigated by safety and tolerability concerns with this agent including weight gain and metabolic syndrome that warrants clinician vigilance and discernment that is imperative in today's clinical practice.

Keywords: olanzapine, bipolar disorder, treatment

Introduction

Bipolar disorder is a common psychiatric illness with a highly variable course and high rates of morbidity and mortality requiring lifelong treatment. It has an estimated prevalence of 1.6%–3.7%, and is an episodic illness interspersed with erratic cycles of mania and depression or mixed episodes (Kessler et al 1997; Hirschfield et al 2003). The complex nature of this malady poses several diagnostic and therapeutic challenges. Bipolar disorder carries a high socioeconomic burden given the rates of suicide (15%), the phasic symptoms resulting in relapses, recurrences, rehospitalization, and decreased productivity resulting in poor quality of life for the consumer. Clinical treatment guidelines provide broad recommendations to help clinicians select appropriate treatment alternatives based on the polarity of an episode, mixed state or psychotic symptoms, number of episodes, prior response to treatment and/or presence of comorbidities.

Substantial advances in the recent years have fostered an expansion in the pharmacological treatment options for bipolar disorder, but optimal management of this devastating illness continues to remain an elusive goal. Best clinical evidence with mood stabilizers including lithium, valproate, lamotrigine, and carbamazepine, as well as the atypical antipsychotics olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole suggests that these agents are more effective for symptoms of mood elevation than for symptoms of depression. Clinical Treatment Guidelines, Expert Consensus and Texas Medication Algorithm Project recommend antipsychotic and

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mood stabilizer monotherapy as well as combination with traditional mood stabilizing medications (APA 2002; Keck et al 2004; Suppes et al 2005). First generation antipsychotics have a role in combination with traditional mood stabilizers for acute mania but appear to worsen depressive symptoms. Their utility is also limited by their side-effect profile, especially extrapyramidal symptoms, tardive dyskinesia and sexual dysfunction. With the introduction of second generation antipsychotic medications, there has been a renewed interest in the utility of this class of medications in managing acute mania, depression, mixed states and maintenance treatment. Our field over the last decade or so has seen a tremendous wealth of data documenting the use of atypical antipsychotics in bipolar mania, depression, mixed states and relapse prevention. So far all antipsychotic agents with the exception of clozapine have been approved for the treatment of acute mania. The beneficial effects of atypical antipsychotics are often mitigated by an increased risk of metabolic abnormalities such as dyslipidemia, hyperglycemia, and diabetes mellitus in a population that is already at a heightened risk for metabolic syndrome and cardiovascular morbidity and mortality. Several agents used in acute and prophylactic mania treatment including lithium, valproate, olanzapine, quetiapine, and risperidone can cause problematic weight gain, which often can set the stage for non-adherence. Treatment non-adherence is a major concern in bipolar disorder with nearly half of individuals being non-adherent to psychotropic medication they are prescribed. Prudent practice demands a good risk benefit analysis in choosing an agent that is efficacious, safe and well tolerated when making clinical decisions.

Olanzapine was the first atypical antipsychotic to receive an indication for acute mania. Olanzapine is currently approved not only for the treatment of schizophrenia, but also for the treatment of acute mania and maintenance and relapse prevention of mania in patients successfully treated with this drug. It is now the most studied medication in randomized clinical controlled trials in bipolar disorder, surpassing lithium in its body of evidence. This paper will critically review available randomized clinical trials utilizing olanzapine in bipolar disorder.

Pharmacology

Olanzapine is a second-generation antipsychotic agent that exhibits a wide array of receptor affinities including 5-HT_{2A-C,3,6,7}, dopaminergic D₁₋₅, muscarinic M₁₋₅, α_1 -adrenergic and histaminergic H₁ receptors (Bymaster et al 1997). These receptor affinities have been shown to relate to

recognized clinical and adverse effects of olanzapine. The primary antimanic and antipsychotic effects are likely regulated by the blockade of dopamine D₂ and serotonin 5-HT_{2A} receptors primarily in the mesolimbic pathway. Olanzapine is relatively nonselective at dopamine receptor subtypes, and it shows selectivity for mesolimbic and mesocortical over striatal dopamine tracts (Casey 1997). Olanzapine exhibits linear pharmacokinetic properties across the clinical dosage range of 0.5 to 20 mg (Callaghan et al 1999). It is well absorbed orally with peak concentrations occurring 4–6 hours after oral administration (Kassahun et al 1997).

Hepatic metabolism and drug-drug interactions

Olanzapine is metabolized rapidly by the cytochrome P450 (CYP) 1A2 system, which accounts for approximately 50%–60% of its metabolism (deLeon et al 2005). The remainder of metabolism occurs through the CYP2D6 system, the flavin mono-oxygenase-3 system, and uridine 5'-diphosphate glucuronosyltransferases (UGTs), possibly UGT1A4 (deLeon et al 2005). Because of its metabolism, the clearance is moderately reduced by CYP1A2 inhibitors such as fluvoxamine and CYP2D6 inhibitors such as fluoxetine, paroxetine and bupropion, and increased by CYP1A2 inducers such as carbamazepine (deLeon et al 2005). Polycyclic aromatic hydrocarbons in tobacco smoke can induce metabolism, and smoking cessation can thus be expected to increase an average patient's drug level by an average of 1.5 fold two to four weeks later (deLeon et al 2005). Olanzapine is excreted primarily in the urine with a mean half-life of 36 hours (Casey 1997).

Efficacy studies

Olanzapine has been shown to be efficacious and is also FDA indicated for both acute and maintenance treatment of bipolar I disorder. These indications are based on a number of clinical trials summarized in Tables 1 and 2.

Acute manic or mixed episodes

Our search resulted in six double-blind studies that evaluated the efficacy of olanzapine compared to placebo, divalproex and haloperidol in acute mania or mixed episodes. In each of these studies, olanzapine was found to be efficacious in the reduction of symptoms related to mania or mixed episodes.

The first of the placebo-controlled trials (Tohen et al 1999) was a three week trial which demonstrated a mean change in Young Mania Rating Scale (YMRS) of –10.26 in

Table 1 Olanzapine in the treatment of acute manic or mixed episodes in bipolar I disorder

Reference	Treatment arms	Duration (weeks)	Mean dose (mg/day)	YMRS change	Percent responders
Tohen et al 1999	Olanzapine	3	14.9	-10.26	48.6%
	Placebo	3		-4.88	24.2%
Tohen et al 2000	Olanzapine	4	16.4	-14.8	65%
	Placebo	4		-8.1	43%
Tohen et al 2002	Olanzapine	3	17.4	-13.4	54.4%
	Divalproex	3	1401.2	-10.4	42.3%
Zajacka et al 2002	Olanzapine	12	14.7	-17.2 ^a	Not reported
	Divalproex	12	2115	-14.8 ^a	Not reported
Berk et al 1999	Olanzapine	4	10	-21.5 ^a	Not reported
	Lithium	4	800	-18.4 ^a	Not reported
Tohen et al 2003	Olanzapine	6	15.0 ^a	-21.3 ^b	72.3% ^b
		12	11.4 ^b	-26.5 ^c	96.3% ^c
	Haloperidol	6	7.1 ^a	-23.5 ^b	74.2% ^b
		12	5.2 ^b	-26.8 ^c	94.1% ^c

^anot a statistically significant difference between groups in the study; these studies also used a mania rating scale that was not the YMRS.

^bvalue from week 6 data.

^cvalue from week 12 data.

Abbreviation: YMRS, young mania rating scale.

Response defined as 50% or more improvement in YMRS.

the olanzapine group and -4.88 in the placebo group, with 48.6% of patients being responders in the olanzapine-treated group compared to 24.2% of the placebo-treated group. Olanzapine at a mean modal dose of 14.9 mg was shown to be superior to placebo in the treatment of acute symptoms of mania in this trial. The limitations to this study were the high drop out rate in the placebo group, and allowance of concomitant use of lorazepam up to 4 mg daily for the first seven days then 2 mg daily for an additional 3 days, which in total constituted almost half of the study length.

In the other double-blind, placebo-controlled trial (Tohen et al 2000) the mean change in YMRS over four weeks in the olanzapine group and placebo group were -14.8 and -8.1 respectively. Sixty-five percent of patients in the olanzapine-treated group were responders compared to forty-three percent in the placebo-treated group. Olanzapine at a mean modal dose of 16.4 mg was shown to be superior to placebo in the treatment of acute symptoms of mania in this trial. This study was one week longer than the previous placebo-controlled trial and allowed lower doses of concomitant

Table 2 Olanzapine in the maintenance treatment of bipolar I disorder

Reference	Treatment arms	Duration (weeks)	Mean dose (mg/day)	Median time to relapse (days)	Relapse rate
Tohen et al 2003	Olanzapine	47	16.2	27 ^a	42.4%
Tohen et al 2004	Divalproex	47	1584.7	27 ^a	56.5%
	Olanzapine + (Li or DV)	78	OLZ = 8.6 Li = 1064.6 DV = 1264.6	163	37% ^b
	Li or DV Monotherapy	78	Li = 1023.8 DV = 1286.5	42	55% ^b
Tohen et al 2005	Olanzapine	52	11.9	Not reported	30.0%
	Lithium	52	1102.7	Not reported	38.8%
Tohen et al 2006	Olanzapine	48	12.5	174	46.7%
	Placebo	48		22	80.1%

Relapse defined as symptomatic recurrence of any affective episode.

^a25th percentile reported instead of median time.

^bnot a statistically significant difference between groups in the study.

Abbreviations: Li, lithium; DV, divalproex sodium.

lorazepam (up to 2 mg daily for first four days then up to 1 mg daily for the next six days). Neither study utilized an active comparator treatment arm.

Two studies (Tohen, Baker et al 2002; Zajecka et al 2002) compared olanzapine to divalproex in the treatment of acute mania or mixed mania. Olanzapine was found to be efficacious in both studies. However, in the study by Tohen, Baker et al (2002), it was determined to be significantly better than divalproex in reduction of manic symptoms, while in the study performed by Zajecka and colleagues (2002), there was no significant differences between the two groups. The main difference between the two studies was in dosing (non-loading versus loading) of the two agents, with the study that showed superiority of olanzapine (Tohen, Baker et al 2002) having initial dosing of olanzapine very similar to the mean modal dose for the study (15 mg/day versus 17.4 mg/day) while initial dosing of divalproex was much lower than the mean modal dose for the study (750 mg/day versus 1401.2 mg/day), suggesting the olanzapine was more effectively dosed from the onset. The study (Zajecka et al 2002) that showed no difference between olanzapine and divalproex also had fewer subjects overall (120 compared to 248), used the Mania Rating Scale instead of the YMRS, and did not report percentage of responders. Since divalproex is considered a first-line treatment for mania, even an equivalent response is sufficient to demonstrate efficacy of olanzapine in mania.

As lithium is still considered the gold standard for bipolar treatment, it is significant to note that a head-to-head trial (Berk et al 1999) comparing fifteen patients given 10 mg total daily olanzapine to fifteen patients given 800 mg daily lithium over a four-week period produced no significant differences in Mania Scale, brief psychiatric rating scale (BPRS), or clinical global impression (CGI) improvement scores. Olanzapine did have a statistically significant superiority to lithium in the CGI severity scale at week 4 in this study. The study does provide some evidence to the assertion that olanzapine is effective in the treatment of mania based on the CGI difference. Given the limitation of a small sample size, larger trials comparing these agents to demonstrate comparative efficacy would be useful to elucidate and support these findings. Also, since a placebo arm was not used in this trial, an assertion of no difference could show merely that the statistical power was not sufficient to separate an effective from an ineffective treatment.

In a study (Tohen, Baker, et al 2003) comparing olanzapine to haloperidol, additional information about the efficacy of olanzapine in mania is reported. The results showed an

increased response rate of >50% improvement in YMRS at 12 weeks compared to 6 weeks for both olanzapine-treated subjects and haloperidol-treated subjects. There were statistically significant differences between the groups with haloperidol faring better in the reduction of manic symptoms by the end of six weeks and olanzapine faring better in the reduction of manic symptoms from week six to week 12, although the groups were statistically similar by week 12. The estimated median time to first remission (defined by a YMRS score of 12 or lower and a HAM-D-21 score of 8 or lower) was 34 days for this group. There were no significant differences in response or remission between the haloperidol and olanzapine groups, except that olanzapine was found to be significantly more effective than haloperidol in patients without psychotic features (56.7% versus 41.6%). The authors suggested the findings might indicate that the anti-manic efficacy of olanzapine is independent of its anti-psychotic properties.

In a 6-week double-blind, randomized trial by Tohen, Chengappa et al (2002) designed to evaluate the efficacy of olanzapine compared to placebo as an augmenting agent for patients with acute manic or mixed bipolar episodes with an inadequate response to at least two weeks of lithium or valproate therapy showed the addition of olanzapine provided superior efficacy to continued monotherapy with lithium or valproate in these patients that were poorly responsive to monotherapy after at least two weeks. Olanzapine augmentation produced superior YMRS improvements (-13.11 versus -9.1 change from baseline; $p = 0.003$) and clinical response rates (67.7% versus 44.7%; $p < 0.001$).

A unique study (Baker et al 2003) that has bearing on use of olanzapine in acute mania studied the effectiveness of rapid initial dose escalation (RIDE) of oral olanzapine versus usual clinical practice in patients with acute agitation. The RIDE method involves use of up to 40 mg olanzapine on days one and two, up to 30 mg on days three and four and 5 mg/d to 20 mg/d after day four. The usual clinical practice method involves use of 10 mg/d olanzapine plus up to 4 mg lorazepam on days one and two and up to 2 mg lorazepam on days three and four then olanzapine 5 mg/day to 20 mg/day after day four. Although this study enrolled patients with psychosis-related diagnoses (71.6% of those enrolled) and bipolar I disorder (28.4%), the results revealed the RIDE group had significant improvements over the usual clinical practice group in controlling acute agitation. These results may be useful in acute mania, though it would be best to have a similar study involving only those patients diagnosed with Bipolar I disorder. The study discussion also questioned whether a higher dosing than the usual

20 mg/day of oral olanzapine prominent in the acute mania trials could provide better mania outcomes.

Maintenance therapy

There are four randomized, double-blind trials investigating the efficacy of olanzapine compared to placebo, lithium or divalproex monotherapy as well as augmentation in maintenance therapy or prevention of relapse of affective episodes in bipolar I disorder. The studies varied in length from 47 to 78 weeks with the dosing and efficacy results summarized in Table 2. These studies help support the use of olanzapine in relapse prevention in bipolar disorder due to the favorable results in efficacy in the olanzapine-treated patients.

Tohen, Ketter et al (2003) compared the efficacy of olanzapine to divalproex, evaluating a total of 251 patients with manic or mixed episodes. Patients with YMRS scores of ≥ 20 were included. Symptomatic remission was defined as a YMRS ≤ 12 while symptomatic relapse was defined as a YMRS ≥ 15 for a manic episode or a Hamilton depression rating scale ≥ 15 for a depressive episode. The study participants initially entered a 3-week study comparing efficacy for acute mania, with responders entering a 44-week double-blind extension period. The 25th percentile of time to relapse was reported in both the olanzapine and divalproex groups as 27 days (Table 2) rather than reporting a median time to relapse. The authors reported that rates of remission were greater in both groups at endpoint than at week 3. Rates of relapse did not differ significantly between the two groups. Because the study was not specifically designed to address relapse prevention, the authors noted limitations in its design. Patients were not in remission at the start of the study, but rather were in an acute manic or mixed episode. Also, the study had a high dropout rate with final relapse rates based on 33 olanzapine-treated patients and 23 divalproex-treated patients.

Tohen and colleagues (2004) compared combination of olanzapine and a mood stabilizer (lithium or divalproex) to mood stabilizer monotherapy. The combination-treated group showed a statistically significant increase (163 days versus 42 days; $p = 0.023$) in time to symptomatic relapse, but did not statistically separate from monotherapy in rate of relapse (37% versus 55%; $p = 0.149$). There was also no significant difference between groups in time to syndromic relapse (94 days versus 40.5 days; $p = 0.742$). One limitation of particular interest is that the patients in the study in the authors' own words, represent an "enriched" sample, because they were required to show incomplete responses to monotherapy and then respond satisfactorily to combination therapy with olanzapine. Also, the mean blood levels

of valproate were on the lower end of the therapeutic range at 67.8 $\mu\text{g/mL}$ in combination therapy and 66.3 $\mu\text{g/mL}$ in monotherapy.

In a study comparing olanzapine to lithium for bipolar relapse prevention for 12 months, Tohen and colleagues (2005) found olanzapine to be statistically non-inferior to lithium. This study enrolled patients with YMRS scores ≥ 20 . The subjects were initially treated with a combination of olanzapine and lithium. Those patients who met symptomatic remission criteria after 6–12 weeks in an open label phase were randomized to monotherapy with lithium or olanzapine. During the next four weeks, the additional medication from the open label phase was tapered and discontinued. The patients were then randomized to receive olanzapine or lithium monotherapy for 48 weeks. In this study, symptomatic recurrence of any mood episode following remission of mania or depression was 38.8% in lithium-treated group and 30.0% in the olanzapine-treated group. In evaluating pole-specific recurrences, there were no statistically significant differences in the proportion of depressive recurrences (15.7% with olanzapine versus 10.7% with lithium; $p = 0.15$) though the trend favored lithium. However, a significantly lower proportion of olanzapine-treated patients compared to the lithium-treated group had recurrence of manic (13.8% versus 23.4%; $p = 0.02$) or mixed episodes (0.5% versus 4.7%; $p = 0.005$). Of note, the mean lithium level in the study is 0.76 mEq/L, which is within, but not near the upper end of, the therapeutic range. It is possible that a higher level would have been optimal for a number of the patients on lithium. Since the design required investigators to optimize lithium dose and reach a target blood level of 0.6–1.2 mEq/L by week 4 and most patients would be below the range initially, some investigators might have hesitated to increase the lithium dose once the target level was reached, resulting in a lower mean lithium level.

The most recent study evaluating efficacy of olanzapine in the prevention of relapse of bipolar disorder affective episodes was a double-blind, placebo-controlled trial of a total of 361 patients (225 given olanzapine, 136 given placebo) for up to 48 weeks (Tohen et al 2006). This study enrolled patients who had achieved stabilization from a manic or mixed episode during 6–12 weeks of open-label therapy with olanzapine. Time to relapse was significantly longer in the olanzapine-treated group than the placebo control (174 days versus 22 days; $p < 0.001$). Also, the relapse rate was significantly lower in the olanzapine-treated group (46.7% versus 80.1%) corresponding to a number needed to treat of 3.0 (95% CI 2.3–4.1), indicating that for every three

patients treated with olanzapine, a relapse would have been prevented for one patient during this time frame.

Based on the studies presented here, there seems to be sufficient data to endorse the use of olanzapine in the maintenance of bipolar disorder, with evidence more clearly positive in prevention of mania and mixed states than in the prevention of depressive episodes.

Bipolar depression

Olanzapine-fluoxetine combination (OFC) therapy and quetiapine are the only FDA approved medications for the treatment of acute bipolar depression. There is some evidence to suggest that olanzapine monotherapy may have some efficacy in depression, though it is clearly less effective than the combination therapy, based on current reported research studies. In a study by Tohen, Vieta et al (2003), the efficacy of olanzapine and OFC therapy were compared to placebo in the treatment of bipolar I depression. The results of the study revealed that both olanzapine monotherapy and OFC were significantly more effective than placebo from week 4 to week 8 in decreasing symptoms of depression and producing response and remission. The limitations of this study included a higher attrition rate and the lack of a fluoxetine monotherapy comparison arm. However, this was the first placebo-controlled trial comparing an antipsychotic or mood-stabilizing agent alone and in combination with an antidepressant agent with the combination demonstrating a robust antidepressant effect with a lower risk of switching to mania. The study had lower rates of discontinuation due to adverse events with improved response and remission rates.

The 2002 American Psychiatric Association practice guidelines recommend lithium or lamotrigine as first-line treatment for bipolar depression (APA 2006). In a 7-week randomized, double-blind study comparing OFC to lamotrigine in the treatment of bipolar depression (Brown et al 2006), OFC demonstrated superior efficacy to lamotrigine in improvement of depressive and manic symptoms in patients with bipolar I disorder. This study did not include a placebo arm and the dose of lamotrigine was escalated to 200 mg while previous studies in bipolar depression had demonstrated both 50 mg and 200 mg of lamotrigine to be effective. In this study treatment differences in illness severity, depressive symptoms and manic symptoms favored OFC over lamotrigine that reached statistical significance as early as week 1. Mean weight gain, dyslipidemias and prolactin elevations were observed in the OFC treated group compared to the lamotrigine treated group. A greater incidence in treatment emergent suicidal and self-injurious behaviors was noticed in the lamotrigine treated

group. This study lent further support for the use of OFC for treatment of bipolar depression.

Safety and tolerability issues

Individuals with severe persistent mental illness are at an increased risk for obesity, diabetes, hypertension, cardiovascular morbidity and mortality (McElroy et al 2002; Faglioni et al 2003; Basu et al 2004; Faglioni et al 2005). Patients with serious persistent mental disorders may be at an increased risk for metabolic issues because of a sedentary lifestyle and poor nutrition, lack of access to adequate medical care, nutrition and exercise programs. The prevalence rate of metabolic syndrome in bipolar disorder ranges from 30%–42%, a proportion higher than the general population but similar to that observed in schizophrenia (30%–42%) (Basu et al 2004; Faglioni et al 2005; Goff et al 2005).

Treatment with a variety of psychotropic medications, including antipsychotics (Masand et al 2005; Newcomer 2005), and mood stabilizers (Ness-Abramof and Apovian 2005) may also result in weight gain. In bipolar disorder, sociodemographic factors associated with age, sex, income level, physical inactivity, comorbid binge eating, and treatment with some psychotropic medications have been identified as clinical predictors of weight gain (Lipkovich et al 2006). Weight gain is a major contributor to medication non-adherence, subsequent relapse and poor prognosis (Brown et al 1999).

Review of evidence-based trials has demonstrated that clozapine and olanzapine are associated with a greater risk of clinically significant weight gain with the other atypicals posing a relatively lower risk. The Consensus Panel guideline also provides some guidance based on evidence-based trials as to the propensity of second generation antipsychotics on weight gain, diabetes and dyslipidemias (ADA 2004). In a study by Lipkovich et al (2006), substantial amount of weight gain with olanzapine at the end of 30 weeks was predicted by weight increases of 2–3 kg within the first 3 weeks of treatment. They also predicted that BMI close to normal ($<27\text{kg/m}^2$) at treatment initiation also was a risk factor for future weight gain (Lipkovich et al 2006). Comparative trials have demonstrated mean body weight is significantly greater in the olanzapine treated group versus lithium, valproic acid and other second generation antipsychotics (Tohen, Baker et al 2002; Zajecka et al 2002; Tohen, Goldberg et al 2003; Baker et al 2003_[TC2]). Weight gain after longer exposure to olanzapine monotherapy was 2 kg compared to the combination of olanzapine with lithium or valproate demonstrating a weight increase of 5–6 kg (Bowden 2003).

Atypical antipsychotics have been associated with obesity and other metabolic comorbidities. Published studies indicate that atypical antipsychotics alter glucose and lipid metabolism. Olanzapine with other atypical antipsychotics is at a substantially higher risk for impaired regulation, weight gain and dyslipidemias. Hyperglycemia caused by olanzapine can progress to frank diabetes and diabetic ketoacidosis. Both acute phase and maintenance trials with olanzapine have demonstrated greater elevations in mean cholesterol and low density lipoprotein, albumin and total protein compared to valproic acid (Zajecka et al 2002; Tohen, Goldberg et al 2003).

In short-term clinical trials 5–20 mg/day of olanzapine compared to placebo was associated with somnolence, dry mouth, dizziness, headaches, dyspepsia, agitation, asthenia, tremor and weight gain (Tohen et al 1999; Tohen et al 2000). There are at least two reported cases of olanzapine-induced pancreatitis (Doucette et al 2000; Waage et al 2004).

Laboratory abnormalities included a higher incidence of elevated liver enzyme values (ALT/SGPT) in the olanzapine group compared to the placebo group (17.6% versus 0%) in one study (Tohen et al 1999). However, all of the ALT/SGPT values returned to normal during continued olanzapine treatment (Tohen et al 1999). A second study revealed a higher incidence of ALT and AST elevations in the olanzapine group compared to the placebo group (21.6% versus 3.9%) with only one (of 55 total) olanzapine-treated patient having the elevations at either end point or two consecutive observations (Tohen et al 2000). No patients in either study displayed clinical symptoms of hepatic dysfunction at any time during the study (Tohen et al 1999, 2000). In studies olanzapine has been shown to transiently elevate serum prolactin levels (Gorobets 2005). There have been no reports of clinically relevant ECG changes with olanzapine (Barak 2005).

Extrapyramidal symptoms were infrequent resulting in negligible use of anticholinergic agents in both short-term and long-term studies (Tohen et al 1999, 2000; Tohen, Baker et al 2002; Tohen, Chengappa et al 2002). Incidence of extrapyramidal symptoms (EPS) is similar between olanzapine and lithium, valproic acid but higher with haloperidol (Berk et al 1999; Tohen, Baker et al 2002; Zajecka et al 2002). It has been suggested that patients with affective disorders are at a higher risk of tardive dyskinesia. Second generation antipsychotics have demonstrated a lower risk of tardive dyskinesia compared to conventional antipsychotics. The risk of tardive dyskinesia with olanzapine in clinical

trials was 1% compared to haloperidol 4.5% (Tollefson et al 1997).

Quality of life, patient satisfaction/acceptability and adherence

The long-term treatment goal of remission and recovery that ultimately results in improved quality of life in Bipolar Disorder should focus on physical, emotional, occupational and social well being of the client. Few studies have evaluated the impact of bipolar disorder on health related quality of life. In a review by Namjoshi et al (2001) bipolar patients seemed to report less satisfaction with their quality of life compared to patients with schizophrenia. This could also be as a result of higher level of education, financial status and overall health status in patients' with bipolar disorder compared to patients with schizophrenia (Atkinson et al 1997). Women tend to report lower scores than men (Vojta et al 2001) while manic/hypomanic patients tend to report lower quality of life compared to euthymic patients. Depressive symptoms also seem to play a role in the evaluation of quality of life (Namjoshi et al 2002).

Studies addressing quality-of-life outcomes with olanzapine in patients with the diagnosis of bipolar I disorder manic or mixed episode included an acute phase followed by a 49-week open-label extension phase during which all patients were treated with olanzapine. The open-label extension allowed the use of lithium or fluoxetine for patients with breakthrough episodes. Health-related quality of life assessment was measured using the Short Form-36 (SF-36) of the Medical Outcomes Study. Olanzapine-treated patients reported significant improvements in manic symptoms as measured by YMRS scores during the 3-week acute phase compared with the placebo-treated group. A significant improvement in the olanzapine-treated patients on the "physical functioning" dimension of SF-36 compared with placebo was evidence. In the 49 week open label extension phase more olanzapine-treated than placebo-treated patients were discharged from the hospital and further improvements on all SF-36 dimensions compared with at the end of the acute treatment period was observed. A correlation between improvements on the YMRS and SF-36, suggested olanzapine treated patients may start to experience functional improvement as well (Namjoshi et al 2002). In other studies olanzapine as an add on to lithium or valproic acid demonstrated combination treatment demonstrated an improvement on the YMRS, HAM-D as well as the Lehrman's quality of life scale; thereby suggesting the benefits of olanzapine in symptom improvement, social functioning and the overall quality of life (Shi 2002).

Patients with a negative attitude toward treatment either due to illness, efficacy or adverse events, are also more likely to be non-adherent. Non-adherence is a common occurrence in patients with bipolar disorder and is often closely linked to relapse and rehospitalization. Comorbid substance abuse, little family involvement, and a poor clinician-patient relationship are among the other risk factors for non-adherence (Revicki 2005).

Strategies for improving adherence

Strategies to improve adherence include optimizing antipsychotic therapy, minimizing adverse events, encouraging patient participation in psychoeducational programs, treating comorbid substance abuse disorders, involving family members in the treatment process, and forging a close therapeutic relationship with the patient.

Selecting an effective antipsychotic that the patient can tolerate is the first step in improving adherence (Krebs et al 2006). Because EPS, weight gain, and sexual dysfunction appear to have the greatest negative impact on adherence, antipsychotics least likely to cause these adverse events should be the first choice for initial treatment. Atypical antipsychotics like olanzapine may be of particular benefit in conjunction with psychoeducational programs because these agents, apart from their efficacy for mood stabilizing effects, positive, negative symptoms, may also improve cognition (Milkowitz 2006).

Improving adherence involves collaboration between the clinician, patient, and family members. Interventions to improve adherence includes optimizing pharmacotherapeutic treatments by incorporating psychosocial strategies. Psychoeducational programs with behavioral interventions based on motivational interviewing, problem solving, supportive services, family education, assertive community training are likely to improve adherence (Milkowitz 2006).

Conclusion

Most published studies on olanzapine have dealt with issues related to efficacy and safety, with a handful devoted to quality of life measures. More recent independently funded studies including the Clinical Antipsychotic Trial of Interventions Effectiveness (CATIE), Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and Systematic Treatment Enhancement Program in Bipolar Disorder (STEP-BD) have focused on effectiveness in terms of important outcomes such as medication-adherence behavior, quality of life, subjective tolerability, and overall satisfaction with treatment. (Goff et al 2005; Rush et al

2006; Nierenberg et al 2006). There is an urgent need for well-designed, controlled, and adequately powered studies before any firm conclusions can be reached. A strong therapeutic alliance, combined with psychoeducation and adequate monitoring of symptoms and adverse effects should serve as a premise for treatment adherence. Multimodal treatment approaches including lifestyle modification including diet and exercise when feasible are more likely to foster adherence since they address a wider array of problem areas. Improving patient adherence to antipsychotic maintenance therapy is crucial to any effort to decrease rates of relapse and rehospitalization in patients with schizophrenia. However, the adverse event profile must be taken into account in reaching a prescribing decision based on weighing the advantages and disadvantages for the individual bipolar patient.

References

- [ADA] American Diabetes Association. 2004. Consensus development and conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*, 27:596–601.
- [APA] American Psychiatric Association. 2002. Practice guidelines for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry*, 159(Suppl 4):1–50.
- [APA] American Psychiatric Association. 2006. Practice guideline for the treatment of patients with bipolar disorder second edition [online]. Accessed Nov 24, 2006. URL: <http://www.psych.org>
- Atkinson M, Zibin S, Chuang H. 1997. Characterizing quality of life among patients with chronic mental illness: a critical examination of the self-report methodology. *Am J Psychiatry*, 154:99–105.
- Baker RW, Kinon BJ, Maguire GA, et al. 2003. Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. *J Clin Psychopharmacol*, 23:342–8.
- Baker RW, Tohen M, Fawcett J, et al. 2003. Acute dysphoric mania: treatment response to olanzapine versus placebo. *J Clin Psychopharmacol*, 23:132–7.
- Barak Y, Swartz M, Plopsy I. 2005. Assessing cardiovascular risks of olanzapine treatment: a 6-month study versus haloperidol in schizophrenia patients. *Int Clin Psychopharmacol*, 20:315–17.
- Basu R, Brar JS, Chengappa KN, et al. 2004. The prevalence of the metabolic syndrome in patients with schizoaffective disorder – bipolar subtype. *Bipolar Disord*, 6:314–18.
- Berk M, Ichim L, Brook S. 1999. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *International Clinical Psychopharmacology*, 14:339–43.
- Bowden CL. 2003. Acute and maintenance treatment with mood stabilizers. *Int J Neuropsychopharmacol*, 6:269–75. Review Journal of Affective Disorders 67, 2001, 257–65.^[TC3]
- Brown EB, McElroy SL, Keck PE Jr, et al. 2006. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *Journal of Clinical Psychiatry*, 67:1025–33.
- Brown JB, Nichols GA, Glauber HS, et al. 1999. Ten-year follow-up of antidiabetic drug use, nonadherence, and mortality in a defined population with type 2 diabetes mellitus. *Clin Ther*, 21:1045–57.
- Bymaster FP, Rasmussen K, Calligaro DO, et al. 1997. In vitro and in vivo biochemistry of olanzapine: a novel, atypical antipsychotic drug. *Journal of Clinical Psychiatry*, 58(Suppl 10):28–36.
- Callaghan JT, Bergstrom RF, Ptak LR, et al. 1999. Olanzapine: pharmacokinetic and pharmacodynamic profile. *Clinical Pharmacokinetics*, 37:177–93.

- Casey DE. 1997. The relation of pharmacology to side effects. *J Clin Psychiatry*, 58(Suppl 10):55–62.
- deLeon J, Armstrong SC, Cozza KL. 2005. The dosing of atypical antipsychotics. *Psychosomatics*, 46:262–73.
- Doucette DE, Grenier JP, Robertson PS. 2000. Olanzapine-induced acute pancreatitis. *The Annals of Pharmacotherapy*, 34:1128–31.
- Fagiolini A, Kupfer DJ, Houck PR, et al. 2003. Obesity as a correlate of outcome in patients with bipolar I disorder. *Am J Psychiatry*, 160:112–17.
- Fagiolini A, Frank E, Scott JA, et al. 2005. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. *Bipolar Disord*, 7:424–30.
- Goff DC, Sullivan LM, McEvoy JP, et al. 2005. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res*, 80:45–53.
- Gorobets LN. 2005. Effect of therapy with atypical antipsychotic drugs on prolactin concentration in patients with schizophrenia and schizoaffective disorders. *Bull Exp Biol Med*, 140:714–15.
- Hirschfeld RM, Lewis L, Vornik LA. 2003. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry*, 64:161–74.
- Kassahun K, Mattiuz E, Nyhart E, et al. 1997. Disposition and biotransformation of the antipsychotic agent olanzapine in humans. *Drug Metab Dispos*, 25:81–93.
- Keck PE Jr, Perlis RH, Otto MW, et al. 2004. Expert consensus guideline series: treatment of bipolar disorder 2004. *Postgraduate Med Special Report*, 12:1–120.
- Kessler RC, Rubinow DR, Holmes C, et al. 1997. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol Med*, 27:1079–89.
- Krebs M, Leopold K, Hinzpeter A, et al. 2006. Current schizophrenia drugs: efficacy and side effects. *Expert Opin Pharmacother*, 7:1005–16.
- Lipkovich I, Citrome L, Perlis R, et al. 2006. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. *J Clin Psychopharmacol*, 26:316–20.
- Masand PS, Culppepper L, Henderson D, et al. 2005. Metabolic and endocrine disturbances in psychiatric disorders: a multidisciplinary approach to appropriate atypical antipsychotic utilization. *CNS Spectr*, 10:(Suppl 14):1–15.
- McElroy SL, Frye MA, Suppes T, et al. 2002. Correlates of overweight and obesity in 644 patients with bipolar disorder. *J Clin Psychiatry*, 63:207–13.
- Miklowitz DJ. 2006. An update on the role of psychotherapy in the management of bipolar disorder. *Curr Psychiatry Rep*, 8:498–503.
- Namjoshi MA, Buesching DP. 2001. A review of the health-related quality of life literature in bipolar disorder. *Qual Life Res*, 10:105–15.
- Namjoshi MA, Rajamannar G, Jacobs T, et al. 2002. Economic, clinical, and quality-of-life outcomes associated with olanzapine treatment in mania. Results from a randomized controlled trial. *J Affect Disord*, 69:109–18.
- Ness-Abramof R, Apovian CM. 2005. Drug-induced weight gain. *Drugs Today (Barc)*, 41:547–55. Review.
- Newcomer JW. 2005. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*, 19 Suppl 1:1–93. Review.
- Nierenberg AA, Istacher MJ, Calabrese JR, et al. 2006. Treatment resistant bipolar depression. A STEP-BD equipose randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol or risperidone. *Am J Psychiatry*, 163:210–16.
- Revicki DA, Matza LS, Flood E, et al. 2005. Bipolar disorder and health-related quality of life: review of burden of disease and clinical trials. *Pharmacoeconomics*, 23:583–94. Review.
- Rush AJ, Trivedi MH, Wisniewski SR, et al. 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*, 163:1905–17.
- Shi L, Namjoshi MA, Zhang F, et al. 2002. Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. *Int Clin Psychopharmacol*, 17:227–37.
- Suppes T, Dennehy EB, Hirschfeld RM, et al. 2005. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *Journal of Clinical Psychiatry*, 66:870–86.
- Tohen M, Baker RW, Altshuler LL, et al. 2002. Olanzapine versus divalproex in the treatment of acute mania. *American Journal of Psychiatry*, 159:1011–17.
- Tohen M, Calabrese JR, Sachs GS, et al. 2006. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *Am J Psychiatry*, 163:247–56.
- Tohen M, Chengappa KN, Suppes T, et al. 2002. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry*, 59:62–9.
- Tohen M, Chengappa KN, Suppes T, et al. 2004. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *British Journal of Psychiatry*, 184:337–45.
- Tohen M, Goldberg JF, Arrillaga AM, et al. 2003. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. *Archives of General of Psychiatry*, 60:1218–26.
- Tohen M, Greil W, Calabrese JR, et al. 2005. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *American Journal of Psychiatry*, 162:1281–90.
- Tohen M, Jacobs TG, Grundy SL, et al. 2000. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Archives of General Psychiatry*, 57:841–9.
- Tohen M, Ketter TA, Zarate CA, et al. 2003. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *American Journal of Psychiatry*, 160:1263–71.
- Tohen M, Sanger TM, McElroy SL, et al. 1999. Olanzapine versus placebo in the treatment of acute mania. *American Journal of Psychiatry*, 156:702–9.
- Tohen M, Vieta E, Calabrese J, et al. 2003. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Archives of General Psychiatry*, 60:1079–88.
- Tollefson GD, Beasley CM Jr, Tran PV, et al. 1997. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry*, 154:457–65.
- Vojta C, Kinosian B, Glick H, et al. 2001. Self-reported quality of life across mood states in bipolar disorder. *Compr Psychiatry*, 42:190–5.
- Waage C, Carlsson H, Nielsen EW. 2004. Olanzapine-induced pancreatitis: a case report. *JOP. J Pancreas (Online)*, 5:388–91.
- Zajecka JM, Weisler R, Sachs G, et al. 2002. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. *Journal of Clinical Psychiatry*, 63:1148–55.

